Ga68-DOTA Peptide PET/CT to Detect Occult Mesenchymal Tumor-Inducing Osteomalacia: A Case Series of Three Patients

Chi Long Ho

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Abstract Tumor-induced osteomalacia (TIO) is a rare disease that manifests with paraneoplastic syndrome and overproduction of fibroblast growth factor 23 (FGF23), leading to renal phosphate wasting and hyperphosphaturia, eventually leading to acquired hypophosphatemic osteomalacia. Diagnosis of this disease is often challenging because of the small size of the lesion, which can be localized in bone or soft tissue anywhere in the body. Detecting these occult mesenchymal tumors (OMT) is of great importance as they are potentially curable after tumor resection. The purpose of this case series is to provide some insight into the diagnosis and localization of OMT associated with osteomalacia, particularly using functional imaging with Ga68-DOTA peptide PET/CT scans.

Keywords Ga68-DOTA peptide or DOTANOC PET/CT · Fibroblast growth factor 23 · Occult mesenchymal tumor · Tumor-induced osteomalacia

Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia (OOM), is a rare acquired paraneoplastic disease associated with benign mesenchymal tumors, with clinical features mimicking those of X-linked or autosomal dominant hereditary hypophosphatemic rickets. TIO was first described in 1947 by Robert McCance; since then, more than 300 cases have been reported in the literature [1, 2]. Detecting these occult mesenchymal tumors (OMT) is of great importance as they are potentially curable after tumor resection.

To date, there are no standard methods for detecting these occult tumors causing oncogenic osteomalacia. Computed tomography (CT) and magnetic resonance imaging (MRI) are often non-contributory in detecting mesenchymal tumors [3]. Bone scintigraphy or radiography only reveals osteomalacia and rarely reveals the mesenchymal tumor causing the symptoms [4]. To the best of our knowledge, only a few reports have evaluated the feasibility of functional imaging in detecting OMT in oncogenic osteomalacia [5]. Here, we report three cases of TIO and evaluate the value of functional imaging with Ga68-DOTA peptide PET/CT scans in identifying the OMT.

Case 1 (Figs. 1 and 2)

A 57-year-old ethnic Chinese female presented to the emergency department with progressively worsening pelvic and bilateral hip pain radiating to her buttocks and thighs. She had a medical history of diabetic mellitus, total hysterectomy with bilateral salpingo-oophorectomy and multiple vertebral compression fractures due to severe osteoporosis for which she was treated with vertebroplasty. She denied any family history of metabolic bone disease. She had sought initial treatment with traditional Chinese medicine but to no avail.

Neurological examination revealed a wheelchair-bound woman with diminished muscle strength of the lower limbs but with sensation preserved. Her gait was significantly limited, reduced by pain and muscle weakness.

Laboratory tests (Table 1) revealed persistent hypophosphatemia and hyperphosphaturia, elevated serum alkaline phosphatase, normal serum calcium and parathyroid hormone levels. Further investigation showed the presence of a high level of serum fibroblast growth factor (FGF) 23 and marginally low level of serum 1,25-dihydroxy-vitamin D. Bone densitometry demonstrated severe osteopenia (Table 1).

C. L. Ho (✉)
Department of Diagnostic Radiology, Singapore General Hospital, 4
Outram Road, Singapore 169608, Singapore
e-mail: clho_2002@yahoo.com

Fig. 1 **a** Plain radiograph of the pelvis shows multiple old fractures of bilateral femoral necks, bilateral superior and right inferior pubic rami. A sclerotic lesion is noted in the left ischial tuberosity. **b** Axial CT image of the lower pelvis shows a sclerotic bone lesion in the left ischial tuberosity, which corresponds to a tracer-avid lesion on (c) axial Ga68-DOTA

peptide PET/CT image. Following resection of the left ischial tuberosity lesion, a follow-up (d) plain radiograph of the pelvis and (e) axial CT image of the lower pelvis show evidence of wide resection with no significant tracer uptake seen at the resection site as noted on the (f) axial Ga68-DOTA peptide PET/CT image

Radiographs of the skeleton revealed bilateral femoral neck and pubic rami fractures, as well as generalized osteopenia, which suggested osteomalacia. In addition, a sclerotic bone

lesion was identified at the left ischial tuberosity (Fig. 1a). Investigation with an 111 -indium octreotide scan failed to localize any focal lesion.

Fig. 2 Before surgical resection, anatomical localization of the lesion was performed by using MRI pelvis. **a** Axial and (c) coronal T1W, (b) axial T2 fat-saturated and (d) axial T1W post-gadolinium images of the pelvis show a heterogeneous enhancing lesion in the left ischial tuberosity with corresponding low signal on T1W and high signal on T2W sequences. **e** Hematoxylin and eosin (magnification $\times 10$) stained section of resected tumor demonstrates numerous spindle cells with pale pink cytoplasm scattered in smudgy to myxoid matrix. There is no significant atypia or pleomorphism

Table 1 Summary of the laboratory and bone densitometry (BMD) tests of three subjects with occult mesenchymal tumors associated with osteomalacia

Variables	Normal range/units	Case 1	Case 2	Case 3	Mean	Interpretation
S.phosphorus	0.81–1.45 mmol/l	0.5	0.6	0.4	0.5	Low
S. calcium	2.1–3.0 mmol/l	2.2	2.5	2.4	2.4	Normal
S. alk. PO4	38–115 IU/l	188	275	394	285.7	High
S. FGF23	<35 pg/ml	362	405	512	426.3	High
S. 1,25DHCC	25–45 ug/l	23.5	26.0	25.0	27.2	Low normal
U. phosphorus	<50 mmol/l	78	62	84	74.7	High
S. PTH	1.2– 5.8 mmol/l	2.4	3.1	2.8	2.8	Normal
BMD	Lumbar	–3.4	–3.1	–3.3	–3.3	Severe osteopaenia
BMD	T score	–4.0	–3.6	–3.5	–3.7	Severe osteopaenia
	Hip					
	T score					

Alk. PO4 = Alkaline phosphatase, BMD = bone densitometry, DHCC = dihydroxy cholecalciferol, FGF = fibroblastic growth factor, PTH = parathyroid hormone, S = serum U = urine

Ga68-DOTA peptide PET/CT scan showed a tracer-avid sclerotic bone lesion in the left ischial tuberosity (Fig. 1b, c). Anatomical localization using magnetic resonance imaging (MRI) confirmed the presence of a well-defined ovoid tumor with heterogeneous enhancement in the left ischial tuberosity measuring 1.2×1.5 cm in diameter (Fig. 2a–d). Surgical excision of this tumor was performed. Histopathologic examination confirmed a mesenchymal tumor of mixed connective tissue origin. FGF-23 staining was performed, and the lesion was consistent with oncogenic osteomalacia.

Five days after tumor removal, the serum phosphorus level normalized to 1.1 mmol/l, and a normal value was maintained in follow-up studies. Musculoskeletal pain and weakness were alleviated 14 days after the operation. The gait function improved, and the serum alkaline phosphatase level normalized.

The follow-up plain radiographs showed evidence of partial resection of the left ischial tuberosity (Fig. 1d) and Ga68-DOTA peptide PET/CT scan (Fig. 1e, f) revealed the absence of a previously noted focus of intense tracer uptake at the resection site.

Case 2 (Fig. 3)

A 26-year-old male of Indonesian Malay origin presented with worsening pain of the left arm and bilateral lower limbs and feet that had started 2 years ago. He had a history of insufficiency fracture of the left hip a few years ago for which he underwent surgery for a hip replacement prosthesis. He denied any family history of

Fig. 3 **a** Coronal CT image of the lower limbs revealed osteopenia of the visualized bones. **b** Sagittal and **(d)** axial CT images of the left ankle and left foot show a lobulated soft tissue nodule in the plantar surface of the left foot, which shows intense tracer uptake on the corresponding Ga68-DOTA peptide PET/CT **(c)** sagittal and **(e)** axial images

metabolic bone disease. Neurological examination revealed an unsteady gait and mild weakness of the left upper and both lower limbs. Laboratory tests revealed hypophosphatemia, raised serum alkaline phosphatase, normal serum calcium and normal parathyroid hormone levels. Hyperphosphaturia and a high level of serum FGF 23 as well as normal levels of serum 1,25-dihydroxy-vitamin D were noted (Table 1). Bone densitometry revealed decreased bone mass in the lumbar vertebrae and right hip, which was compatible with severe osteopenia.

CT scans revealed osteopenia of the bones in the lower limbs and a lobulated soft tissue nodule in the plantar surface of the left foot, which demonstrated intense tracer uptake on the Ga68-DOTA peptide PET/CT scan. After 6 months following treatment, he was asymptomatic with normal serum phosphate levels.

Case 3 (Fig. 4)

A 59-year-old ethnic Chinese female presented with recent onset of right hip pain. She has a history of persistent lower back pain for 10 years. A previous Tc-99m MDP whole-body bone scan showed multiple foci of increased tracer uptake in the axial and appendicular skeleton, which were attributed to previous insufficiency fractures. She did not have a family history of bone disease. Clinical examination results were essentially normal, excluding bone and muscular abnormalities.

Laboratory tests revealed marked hypophosphatemia, hyperphosphaturia and elevated alkaline phosphatase but normal serum calcium and parathyroid hormone levels. Further investigation showed high serum FGF23 and normal serum 1, 25-dihydroxy-vitamin D levels.

Bone densitometry revealed decreased bone mass in the lumbar vertebrae and left hip, which was compatible with

severe osteopenia. Initial investigation with ¹¹¹-indium octreotide failed to localize any lesion.

With the clinical diagnosis of hypophosphatemic osteomalacia, a Ga68-DOTA peptide PET/CT scan was performed to detect the occult tumor causing osteomalacia, and it revealed an isolated sclerotic focus of hypermetabolism in the greater trochanter of the right femur. No other abnormal finding was found in the rest of the imaged body.

Three months following treatment, the serum phosphorus level was normalized to 0.9 mmol/l, and a normal value was maintained in the follow-up study. Her lower back and right hip pain was alleviated subsequently.

Discussion

TIO is related to mesenchymal or mixed connective tumors that markedly overexpress FGF23, which is produced by osteogenic cells, osteoblasts and osteocytes [6, 7]. By exerting an inhibitory activity on the type IIa and IIc sodium-phosphate co-transport system in proximal tubules, FGF23 inhibits renal 1 α -hydroxylation of 25-hydroxyvitamin D, thus promoting hyperphosphaturia [6–8]. Excessive FGF23 action is therefore known to cause severe hypophosphatemia, whereas its deficiency has been found to result in hyperphosphatemic tumoral calcinosis [7]. As in our three reported cases, the biochemical hallmarks of TIO are characterized by renal phosphate wasting and hyperphosphaturia, which lead to acquired hypophosphatemic osteomalacia [6, 7].

Although TIO lesions can be localized in the soft tissue, it occurs more commonly in the bone. Muscle weakness and bone pain are usually the first clinical manifestations [9]. Owing to a lack of knowledge of the existence of TIO, the time from the onset of symptoms until diagnosis is often long. As a result, adults frequently present with multiple insufficiency fractures, vertebral height loss and generalized debilitated status, reminiscent of how patients in the past would present with

Fig. 4 **a** Coronal and **(b)** axial Ga68-DOTA peptide PET/CT images show a tracer-avid lesion in the greater trochanter of the right femur, which is compatible with a somatostatin-receptor expressing tumor. **c** Axial CT image of the pelvis shows a sclerotic focus in the greater trochanter of the right femur, which corresponds to the aforementioned tracer avidity on the Ga68-DOTA peptide PET/CT

advanced primary hyperparathyroidism. If the condition develops before growth plate closure, it can present with skeletal deformities, growth retardation and gait problems and even rickets in children [1, 10].

⁹⁹Tc-MDP bone scintigraphy often reveals multiple foci of uptake at areas of insufficiency fractures or pseudofractures, which may actually misdirect the effort to localize the tumor. Importantly, this finding should not be misinterpreted as evidence of metastatic tumor. We therefore share our experience with previous authors that bone scintigraphy has not proven to be a useful study for localizing TIO [4].

TIO is counted among the ranks of endocrine neoplasms that have a striking presentation. Complete tumor resection is almost always curative as it leads to a dramatic and satisfying resolution of symptoms with rapid improvement, some as early as postoperative day 3 [13]. Moreover, complete tumor resection is of utmost importance to avoid recurrence or metastasis [11]. Nevertheless, it is the return of serum phosphate levels to normal after tumor resection that confirms the diagnosis of TIO [12, 13].

Localization of TIO lesions is however a challenging task as these lesions are usually very small in size and frequently undetectable on clinical examinations [10]. It can be situated in the bone or soft tissue anywhere in the body from head to toe.

According to some authors, patients with TIO-like syndrome who have failed tumor localization at least once at their primary institution were referred to higher institutions. Having been through all the necessary investigations, a group of patients remains for whom a tumor is never found [1, 14].

Some authors advocate F18-fluorodeoxyglucose (FDG) positron emission tomography (PET) with computed tomography (FDG-PET/CT) for localizing TIO [5, 10]. While FDG-PET/CT may be very sensitive, it is non-specific and may identify areas of increased metabolic activity that are not related to the tumor [5]. This is especially true in patients with many areas of active fracture healing.

Another important imaging modality is ¹¹¹-indium octreotide scintigraphy, ideally combined with single photon emission CT (SPECT) [4, 10]. Somatostatin receptors have been found to be present in many TIO lesions, and ¹¹¹-indium octreotide has a high affinity for the somatostatin receptor, especially subtype 2 and to a lesser extent subtype 5 [13, 15]. As with FDG PET/CT, emphasis should be placed on making sure these imaging tests cover the entire body from head to toe, including the hands and feet. Limitations of conventional PET/CT and octreotide scans are that some portions of the extremities and head may be inadvertently excluded during scanning. Additional co-registration of CT to both FDG-PET and octreotide scans may significantly increase the ability to localize tumors, and, whenever possible, it should be performed [4].

Once suspicious lesions have been identified with functional imaging, one could proceed to anatomical imaging to confirm the location of the tumor. Anatomic imaging studies include X-rays, CT and/or MRI scans. Some investigators advocate total body MRI as an initial imaging modality, although we do not believe this to be beneficial as total body MRI is time consuming and may not be feasible for severely ill patients and children to complete the whole examination in the same sitting [5].

In our study, we found a particularly useful combination of functional and anatomical imaging in Ga68-DOTA peptide or DOTANOC PET/CT for localizing TIO lesions. Having been explored by previous authors, Ga68-DOTA peptide or DOTANOC PET/CT combines the specificity of octreotide scanning with the sensitivity of PET/CT [3, 13]. Moreover, it utilizes a modified octreotide molecule (DOTANOC) that has high affinity for both somatostatin receptor 2 and 5 [3, 12, 13]. Labeling this compound with the positron emitter, Ga68, results in a PET compound that is more specific than FDG in localizing lesions of neuroendocrine origin. From our previous experience, ¹¹¹-indium octreotide scans failed to localize a TIO lesion, which was subsequently localized using a Ga68-DOTA peptide PET/CT scan.

It should be noted, however, that there are ‘blind’ spots in this functional imaging modality, for example, the brain uptake of FDG-PET tracer may obscure intracranial tumors, and uptake of octreotide in the liver and spleen may obscure potential lesions within these organs [3, 4, 13, 15].

With this case series, we hope that there will be greater awareness and recognition of TIO as a disease entity and improved localization strategies for this lesion in the future. Large sample studies can be performed by comparing Ga68-DOTA peptide or DOTANOC PET/CT with other conventional imaging modalities for localizing TIO lesions.

In summary, TIO should always be considered as a potential diagnosis in patients presenting with severe weakness of the extremities and musculoskeletal pain. As clinical and biochemical changes of TIO are potentially reversible by tumor removal, localization of these small lesions is challenging but essential. In our study, we found the combination of functional and anatomical imaging in Ga68-DOTA peptide or DOTANOC PET/CT to be extremely useful for localizing TIO lesions.

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Conflict of Interest Chi Long Ho, the author of this manuscript, declares that he has no conflict of interest.

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

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